HLA antigens in chronic relapsing idiopathic inflammatory polyneuropathy

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SUMMARY Observations are reported on 14 patients with a clinical diagnosis of recurrent or chronic relapsing idiopathic inflammatory polyneuropathy of Guillain-Barré type. The results suggest the possibility of a disease susceptibility gene for this disorder associated with the HLA-A1, -B8, -DRw3, and -Dw3 haplotype.

Most cases of idiopathic inflammatory polyneuropathy exhibit an acute monophasic illness (Guillain-Barré syndrome). Recurrences are uncommon. Other clinically similar cases display a more gradual onset and show a chronic relapsing or chronic progressive course. As in the acute disease, they are characterised by predominantly motor involvement, severely reduced nerve conduction velocity, and raised cerebrospinal fluid protein levels. The histological features are similar in the acute and both the chronic relapsing (Thomas *et al.*, 1969) and chronic progressive (Dyck *et al.*, 1975) forms, with extensive segmental demyelination in peripheral nerve trunks and spinal roots associated with focal accumulations of mononuclear cells. It has, therefore, been suggested that these disorders are variants of the same condition (Thomas *et al.*, 1969).

There are close parallels between experimental allergic neuritis (EAN) and the Guillain-Barré syndrome. Experimental allergic neuritis probably represents a cell-mediated, delayed hypersensitivity reaction to peripheral nerve antigens and provides a useful animal model for the Guillain-Barré syndrome (Arnason, 1975). The usual pattern in EAN is an acute monophasic illness, but a small proportion of animals pursue a chronic progressive or relapsing course (Pollard *et al.*, 1975). It is thus possible that the latter parallel the chronic relapsing human cases.

The HLA associations that have been established for a number of autoimmune disorders prompted us to examine the situation in idiopathic demyelinating neuropathy. In 59 cases of the Guillain-Barré syndrome of acute onset, we found no deviation in the frequency of HLA-A, -B or -C antigens (Adams *et al.*, 1977). The lack of any such association has since been confirmed in two further reports (Latovitski *et al.*, 1978; Stewart *et al.*, 1978).

In this communication, we present preliminary results on the distribution of HLA-A, -B, -C, -DR, and -D locus antigens in a series of patients with recurrent or chronic relapsing idiopathic inflammatory polyneuropathy.

Results

The observations were made on 14 cases diagnosed as recurrent or chronic relapsing idiopathic inflammatory polyneuropathy on the basis of their clinical features, raised CSF protein level, nerve conduction studies, and, in some instances, sural or radial nerve biopsy. It was difficult to distinguish recurrent cases—that is, with recovery between episodes—from chronic relapsing cases without recovery between exacerbations. Both variants have, therefore, been included together. All cases had at least two relapses.

Eight HLA-DR antigens were defined by a panel of selected antisera used in the 1977 Histocompatibility Workshop (Bodmer *et al.*, 1978). The HLA-D specificities were identified by the use of homozygous typing cells accredited in the 1975

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and 1977 Histocompatibility Workshops (Thorsby and Piazza, 1975; Festenstein *et al.*, 1978). Each patient was tested at least twice for eight specificities (HLA-Dw1-Dw8), and at least two Dw3 cells were incorporated in each experiment.

The HLA-A, -B, -C, -DR, and -D phenotypes for each patient are given in Table 1. There was a significant increase ($P<0.02$) in the frequency of HLA-B8 (50%) as compared with 25% in a control panel of 571 individuals (Adams *et al.*, 1977). The frequency of the HLA-D region antigens is given in Table 2. When compared with the frequencies in 351 European Caucasoids, there was a significant increase in HLA-DRw3 (50% versus 17%, $P<0.05$). The frequency of HLA-Dw3 was also increased (37% versus 21%, $P<0.05$). Although it was not possible to establish the individual haplotypes without family segregation studies, it is interesting to note that of the five individuals who were HLA-A1, -B8, and -Dw3, three were also HLA-DRw3. However, both HLA-Dw3 and -DRw3 specificities are among those that are not yet clearly defined (Bodmer *et al.*, 1978; Festenstein *et al.*, 1978). HLA-B8, which has the strongest association, is a well-established specificity.

Table 1 Frequency of HLA antigens in patients with chronic relapsing idiopathic inflammatory polyneuropathy

Case	HLA-			HLA-DRw	HLA-Dw
	A	B	Cw		
RD	1,11	27,8	2	6	(3)7
UB	2,24	7,17	—	2,7	7
NP	3,X	w51,8	—	1,3	1,3
WC	1,24	w51,8	—	3	6,3
AW	2,3	7,X	X,X	3	2,4
BS	2,31	w14,w35	4	1,5	—
GA	2,X	w39,w44	4	8	8,—
JG	1,3	8,w35	4	3	1,3
IC	1,X	8,X	—	3	3
GB	2,X	w37,40	3	3,7	4,6
JL	2,11	w35,12	—	5,7×4	—
VB	1,3	8,40	3	3,6	3,6
JR	3,24	8,14,2	—	6	6
MP	3,9	7,40	3	—	—

Table 2 Distribution (percentage values) of HLA-D region antigens in chronic relapsing idiopathic inflammatory polyneuropathy

		Specificity							
		w1	w2	w3	w4	w5	w6	w7	w8
HLA-DW	Patients (14)	14	7	37	21	—	28	14	7
	Control (99)*	10	18	17	21	15	ND	17	ND
HLA-DR	Patients (14)	21	7	50	—	14	21	21	7
	Control (351)†	14	21	17	23	30	17	27	15

*European Caucasoids Histocompatibility Testing 1977, p. 362.

†Histocompatibility Testing 1977, p. 67.

Discussion

These results suggest the possibility of a disease susceptibility gene for cases of recurrent and chronic relapsing idiopathic inflammatory polyneuropathy associated with the HLA-A1, -B8, -DRw3, and -Dw3 haplotype. These preliminary findings need to be confirmed in view of the relatively small number of cases examined and the borderline increased frequencies. On the other hand, they are supported by the findings of Stewart *et al.* (1978), who found a similar trend for an association with HLA-B8 and -DRw3 in 16 cases of chronic relapsing idiopathic polyneuritis. No significant associations were demonstrated for 22 cases of acute Landry-Guillain-Barré syndrome and six cases of subacute polyneuritis.

Stewart *et al.* (1978) also found an increase in HLA-Aw30 and -Aw31 which was not present in our series. Only one of the 14 was HLA-Aw30 or -Aw31. Since there is no linkage disequilibrium between HLA-Aw30/31 and -B8, -Dw3 and -DRw3, the increased frequency raises the possibility of another disease susceptibility gene associated with these two HLA-A locus antigens. A more likely explanation is that the increased frequency is either a chance finding or spurious. Several sera that are used in the definition of these two antigens which are difficult to define may also give positive reactions in the presence of homozygous HLA-A2 cells (Wolf *et al.*, 1975). Thus the apparent A locus phenotype A2, Aw30/31 may in fact be HLA-A-2, -2.

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